Review

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Cellular senescence in liver diseases: From molecular drivers to therapeutic targeting

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Summary

Obesity, metabolic syndrome, and aging are major contributors to the rising global burden of chronic liver diseases. Among these, aging remains an often underrecognised driver that intersects with other metabolic and environmental insults to exacerbate liver dysfunction. Cellular senescence, a key hallmark of aging, is increasingly implicated as a central mechanism linking these risk factors to liver pathophysiology. Senescent cells accumulate across diverse hepatic cell types and influence disease progression and systemic health through their SASP (senescence-associated secretory phenotype). While senotherapeutic strategies, including senolytics and senomorphics, show promise, their efficacy and safety remain highly dependent on cell type, disease context, and agent specificity. Recent advances, such as multi-omics profiling, multi-marker gene signatures, and targeted modalities including PROTACs (proteolysis targeting chimeras) and CAR (chimeric antigen receptor) T-cell therapies, offer new opportunities for precision interventions. This review synthesises emerging insights into the molecular mechanisms of liver senescence, evaluates the current landscape of senotherapies, and outlines key challenges and future directions for safely and effectively targeting senescence in chronic liver disease.

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Introduction

Obesity, metabolic syndrome, and aging are major risk factors for a broad spectrum of chronic liver diseases, which typically follow a progressive trajectory from steatosis and inflammation to fibrosis, cirrhosis, and ultimately liver failure or cancer.[1] While metabolic drivers have garnered increasing attention, aging remains an underappreciated yet fundamental contributor that amplifies liver vulnerability and disease severity. With global life expectancy on the rise, understanding how aging intersects with metabolic and environmental stressors to influence liver disease has become an urgent biomedical priority.

Among the hallmarks of aging, cellular senescence has emerged as a key mechanism linking age-related physiological decline to chronic liver injury and dysfunction.[2–4] Cellular senescence is a stress-induced cell fate characterised by stable cell cycle arrest, resistance to apoptosis, and acquisition of a bioactive senescence-associated secretory phenotype (SASP).[5] While initially regarded as a tumour-suppressive mechanism that halts the proliferation of damaged cells, senescence is now recognised to play dual roles: protective in acute settings, but detrimental when senescent cells persist. In the aging or chronically injured liver, the long-term accumulation of senescent cells fosters a pro-inflammatory and fibrotic microenvironment that promotes tissue dysfunction and disease progression.[2–4]

Accumulating evidence indicates that senescent cells are present across multiple liver-resident cell types, including hepatocytes (which perform key metabolic and detoxification functions), cholangiocytes (which line the bile ducts and regulate bile flow), hepatic stellate cells (HSCs; central mediators of fibrosis), liver sinusoidal endothelial cells (LSECs; gatekeepers of microvascular exchange), and liver-resident macrophages (Kupffer cells).[3,6] Each of these cell types exhibits unique senescence phenotypes and pathological responses to injury or aging. The diversity and context-dependent roles of senescence underscore its complexity and relevance to liver homeostasis and disease.

Recent advances in high-throughput transcriptomics, single-cell and spatial profiling, and lineage-specific genetic models have significantly enhanced our understanding of senescence dynamics in the liver (Box 1). In this review, we synthesise current insights into the molecular mechanisms underlying hepatic cell senescence, characterise its impact across different liver cell types, evaluate the therapeutic potential of senescence-targeted interventions, and highlight key challenges and opportunities for future research aimed at mitigating liver disease and promoting systemic health.

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Keypoints

- Senescence affects multiple hepatic cell types, including hepatocytes, stellate cells, and cholangiocytes, with context-dependent outcomes ranging from tissue repair to fibrosis and tumour promotion.
- The senescence-associated secretory phenotype drives both beneficial and detrimental paracrine effects, shaping liver regeneration, immune responses, and fibrogenesis.
- While senescence initially prevents tumourigenesis via cell cycle arrest and immune surveillance, persistent senescent cells can promote hepatocellular carcinoma and cholangiocarcinoma by fostering immune evasion and a pro-tumourigenic microenvironment.
- Hepatocyte senescence is a reversible and plastic state that can lead to regeneration, fibrosis, or malignant transformation depending on environmental cues and immune competence.
- Conventional markers such as p16 and p21 lack specificity; novel hepatocyte-specific transcriptomic signatures (*e.g.* AHGS, SHGS) provide more accurate tools for detecting and tracking senescence in liver disease.
- Senolytic and senomorphic therapies offer promising avenues for intervention but require further refinement to achieve safe, effective, and cell-type–selective targeting in liver diseases.

Characteristics and key mechanisms of liver senescence

Cellular senescence in the liver is a complex, multifactorial process triggered by a variety of insults, including hepatotoxins, genetic mutations, lipotoxicity, and chronic viral infections, such as hepatitis B and C. Despite the heterogeneity of these stimuli, senescence in hepatic cells converges on a core set of conserved molecular pathways that initiate and maintain the senescent phenotype (Fig. 1).

Growth arrest and cell cycle inhibition

A defining feature of senescent cells is permanent cell cycle arrest, mediated primarily by the p53-p21^{CIP1} and p16^{INK4a}-Rb pathways. In response to hepatic stressors, such as DNA damage or oxidative injury, the DNA damage response is activated, leading to ATM/ATR kinase signalling, p53 stabilisation, and induction of p21, which inhibits cyclin-dependent kinases (CDKs) and halts the G1/S transition. Concurrently, the p16-Rb axis prevents CDK4/6-mediated Rb phosphorylation, further reinforcing growth arrest by blocking E2F-driven transcription.[7,8] Additional molecules, including ARF, CHK1/2, and GADD45, may also participate depending on the senescence-inducing stimulus.[7,8] Notably, while growth arrest is a necessary feature of senescence, it is not sufficient to produce the terminally senescent phenotype, highlighting the need for complementary markers to distinguish senescence from transient quiescence or terminal differentiation.[7,8]

Box 1. State of the field in liver senescence.

- Senescence is multicellular: Senescence affects multiple hepatic cell types, including hepatocytes, HSCs, and cholangiocytes, each contributing uniquely to disease progression.
- Dual role of senescence: Depending on cell type and context, liver senescence can be protective (*e.g.* limiting fibrosis, promoting tissue repair) or deleterious *(e.g.* driving chronic inflammation, fibrosis, and tumorigenesis).
- The SASP is a key mediator: Senescent cells exert potent paracrine effects through the SASP, shaping both the local liver microenvironment and systemic organ function.
- Limitations in senescence detection: Current senescence markers (e.g. p16; p21) are neither specific nor sufficient, complicating the precise identification and targeting of senescent cells *in vivo*.
- Emerging interest in senotherapies: Senotherapeutic strategies, including senolytics and senomorphics, show considerable promise, but their efficacy remains highly cell type, context, and agent-dependent, with significant safety concerns limiting clinical translation.

HSCs, hepatic stellate cells; SASP, senescence-associated secretory phenotype.

Senescence-associated secretory phenotype

Consistent with observations in other tissues, senescent liver cells also adopt SASPs, characterised by the sustained release of pro-inflammatory cytokines, chemokines, growth factors, proteases, and extracellular matrix-modifying enzymes. However, SASPs are not monolithic. Their composition, magnitude, and biological consequences vary significantly depending on the cell type, tissue microenvironment, initiating stressor, and disease stage.[9] In the liver, for instance, hepatocyte-derived SASPs differ markedly from those of non-parenchymal cells and may shift over time from immune-activating to immune-evasive or pro-fibrotic profiles. While transient SASP expression may support tissue repair by promoting immune-mediated clearance of damaged cells, persistent SASP signalling in aging or chronic liver disease drives maladaptive remodelling, fibrogenesis, and systemic metabolic dysfunction.[9–13] A key challenge is to move beyond viewing the SASP as a uniform or static output of senescence. Pathways such as NF-κB, mTOR, TGFβ, and cGAS-STING regulate distinct facets of SASP induction and persistence, with their influence likely evolving over the course of liver disease.[9–13] Notably, activation of the cGAS-STING axis by cytoplasmic mitochondrial DNA (released during mitochondrial stress) is a critical driver of the SASP and has been implicated in senescence-associated inflammation across hepatic and extrahepatic tissues.[14,15]

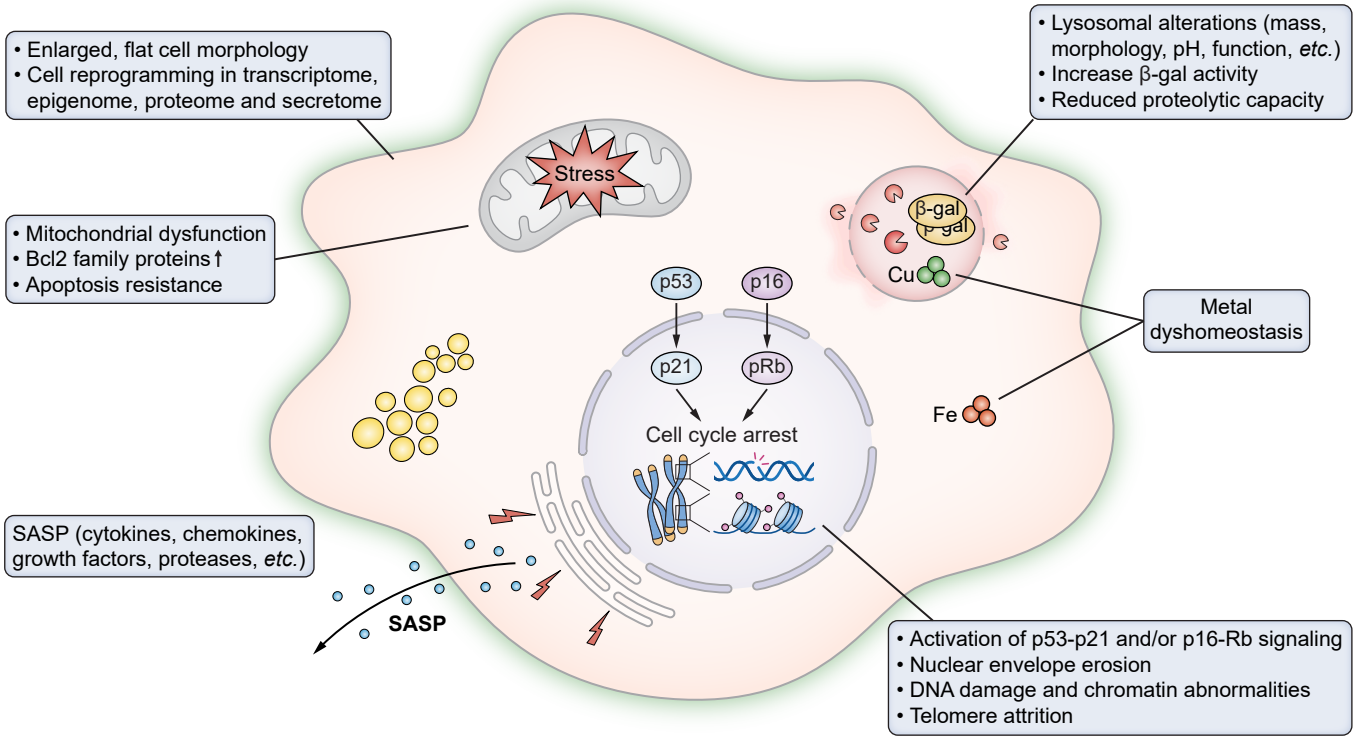

Fig. 1. Hallmarks of cellular senescence in liver cells. Cellular senescence in the liver is triggered by diverse stressors, including telomere attrition, oxidative damage, DNA lesions, and metabolic insults such as lipotoxicity. Senescent liver cells exhibit hallmark morphological features, including cellular enlargement and a flattened shape, along with broad reprogramming of the transcriptome, epigenome, proteome, and secretome. Mitochondrial dysfunction is a key upstream driver and characterised by impaired autophagy, reduced bioenergetic capacity, and elevated expression of anti-apoptotic BCL-2 family proteins. Lysosomal alterations, including changes in mass, pH, morphology, and proteolytic activity, are accompanied by increased β-galactosidase activity, a classical marker of senescence. Metal dyshomeostasis, particularly involving copper and iron, has emerged as a novel driver by exacerbating oxidative stress and lysosomal injury. These organellar perturbations converge on conserved pathways, especially the p53/p21 and p16/Rb signalling axes, to induce irreversible cell cycle arrest. Senescent liver cells also acquire a robust SASP comprising pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodelling enzymes. The SASP reinforces the senescent state, disrupts the local tissue microenvironment, and contributes to systemic dysfunction. SASP, senescence-associated secretory phenotype.

Embracing this conceptual shift is essential for accurately interpreting the role of senescence in liver pathophysiology and for designing selective, stage-appropriate interventions that target senescent cells without disrupting beneficial tissue responses.

Mitochondrial dysfunction and oxidative stress

Mitochondrial dysregulation serves as both a trigger and downstream amplifier of cellular senescence in the liver. Dysfunctional mitochondria are a major source of reactive oxygen species (ROS), which exacerbate genomic instability, DNA damage, and activation of the SASP.[16–18] Conversely, senescent liver cells often exhibit impaired mitophagy and reduced mitochondrial biogenesis, leading to the accumulation of damaged, ROS-producing mitochondria, thereby reinforcing the senescent state in a feed-forward loop.[16–18] Recent studies also demonstrate that mitochondrial DNA released into the cytosol can activate the cGAS-STING pathway, linking mitochondrial stress to pro-inflammatory innate immune signalling and further propagation of senescence within the hepatic microenvironment.[19–21]

Telomere dysfunction

Telomere attrition is a well-established trigger of cellular senescence, particularly in chronically injured or aging tissues. Hepatic cells subjected to oxidative or replicative stress often show telomere shortening, leading to activation of the DNA damage response and stabilisation of p53 and p21 pathways. In hepatocytes, reduced telomerase activity and shortened telomeres have been implicated in the onset of senescence and the progression of cirrhosis.[22] Notably, individuals with longer telomere length show a reduced risk of MASLD onset,[23] whereas shortened leukocyte telomere length has been independently associated with advanced liver disease in older adults and with higher all-cause mortality in patients with liver disease.[24]

Apoptosis resistance

Another hallmark of senescent cells is their resistance to apoptosis, which contributes to their persistence in chronically diseased livers. This phenotype is primarily driven by upregulation of pro-survival pathways, particularly the BCL-2 family of proteins.[25] By evading programmed cell death, senescent

hepatic cells can accumulate over time and maintain a pro-inflammatory and fibrogenic environment. Consequently, many senolytic agents target BCL-2 family members to restore apoptotic susceptibility in senescent cells. However, the expression of these survival factors varies across hepatic cell types and disease stages,[26,27] underscoring the need for cell type- and context-specific senolytic approaches. As such, apoptosis resistance represents both a critical feature of liver senescence and a potential therapeutic vulnerability.

Lysosomal dysfunction and metal dyshomeostasis

Senescent cells exhibit prominent lysosomal expansion and increased activity of senescence-associated β-galactosidase (SA-β-gal). These lysosomes often show impaired autophagic flux and pH regulation, diminishing the cell's ability to degrade damaged organelles.[28,29] Recent studies, including our own, suggest that accumulation of metals such as copper in lysosomes can disrupt lysosomal integrity, promote oxidative damage, and reinforce senescence through lysosomal membrane permeabilisation and cathepsin release.[27,30,31]

Global cell reprogramming

Senescent hepatic cells undergo extensive transcriptional, epigenetic, proteomic, and secretory reprogramming that stabilises the senescent phenotype and contributes to disease progression. Epigenetic alterations include formation of senescence-associated heterochromatin foci, global DNA hypomethylation or locus-specific hypermethylation, and changes in histone modifications that reinforce cell cycle arrest.[32–34] These chromatin changes reprogramme the transcriptome toward pro-inflammatory, pro-fibrotic, and metabolically altered states.[35,36] At the proteomic level, senescent cells show changes in metabolic enzymes, stress response proteins, and regulators of redox balance and autophagy, reflecting a shift in cellular priorities from proliferation to survival and SASP production.[37,38] The secretome, including soluble SASP components and extracellular vesicles, contributes to paracrine signalling, immune recruitment, and secondary senescence in neighbouring cells.[37,38] Single-cell transcriptomics in liver tissue has revealed diverse clusters of senescent cells with distinct molecular features and functional outputs.[27,39,40] Post-transcriptional regulators, such as RNA-binding proteins and non-coding RNAs (*e.g.* microRNAs and long non-coding RNAs), further refine this reprogramming and may serve as biomarkers or therapeutic targets.[41,42]

Senescence across liver cell types: from discovery to therapeutic implications

Cellular senescence is increasingly recognised as a dynamic and multifaceted process affecting multiple hepatic cell types, including hepatocytes, cholangiocytes, HSCs, Kupffer cells, and LSECs.[3,6] The induction, phenotype, and consequences of senescence in these cell populations are highly context-dependent, shaped by the nature of liver injury, disease stage, and local microenvironmental cues. In the sections that follow, we summarise current evidence of senescence across major liver cell types, examine their distinct contributions to liver physiology and pathology, and assess the therapeutic potential of targeting senescent cell populations in various liver diseases (Fig. 2).

Senescence in hepatocytes

As the predominant parenchymal cell type in the liver, hepatocytes play central roles in systemic metabolism and energy homeostasis.[43–45] Due to their high metabolic activity and constant exposure to circulating toxins and inflammatory mediators, hepatocytes are particularly vulnerable to a range of senescence-inducing stressors, including xenobiotics, lipotoxicity, genotoxic injury, and microbial infections. Transcriptomic profiling of aged murine hepatocytes has identified a distinct senescence-associated gene signature enriched in pathways related to ferroptosis, cellular stress, and degenerative processes.[46] Notably, this gene signature is also detectable in liver tissue from human MASLD cohorts, where it correlates with markers of disease severity,[46] suggesting that hepatocyte senescence is not merely a feature of aging but may play an active role in disease pathogenesis. Indeed, during chronic liver injury, hepatocytes exhibit reduced proliferative capacity, persistent stress responses, and acquisition of a robust SASP.[46] Supporting this, our recent studies also demonstrated that senescent hepatocytes can not only impair liver regeneration after liver injury, but also trigger pathogenic reprogramming of other liver cells, including spreading senescence to surrounding non-senescent hepatocytes and promoting HSC fibrogenesis, macrophage activation and LSEC capillarisation, thus reconfiguring the liver microenvironment to promote disease progression.[27] Thus, although they may comprise only a small fraction of total hepatic cells, senescent hepatocytes exert an outsized influence on liver homeostasis and disease evolution (Fig. 3).

Hepatocyte senescence in MASLD

Hepatocyte senescence is particularly relevant in MASLD, where it is closely linked to metabolic syndrome, cirrhosis and adverse clinical outcomes.[34,47,48] Hallmarks of hepatocyte senescence in MASLD include enlarged nuclei (karyomegaly), increased polyploidy, reduced cell cycle activity, telomere attrition, and elevated expression of p21 and p16, often accompanied by DNA damage markers such as γ-H2AX and DNA damage foci.[34,47,48] However, these features have largely been identified through histological or immunohistochemical methods, which provide limited insight into the broader transcriptional and functional diversity of senescent hepatocytes. Moreover, identifying and characterising senescent hepatocytes *in situ*, especially at single-cell resolution, remains a significant challenge due to their heterogeneous phenotypes and the lack of highly specific molecular markers.[7,49] To address these limitations, we recently developed a hepatocyte-specific senescent gene signature (SHGS) using integrative *in vitro* and *in vivo* models.[27] SHGS captures the core transcriptional features of senescent hepatocytes and enables robust deconvolution of bulk and single-nucleus transcriptomic data from human MASLD cohorts.[27] SHGS-positive hepatocytes exhibit loss of liver-specific functional genes and upregulation of inflammatory and fibrogenic SASP components.[27] Functional studies further revealed that these cells can influence neighbouring hepatic cells through paracrine signalling, thereby amplifying disease progression.[27]

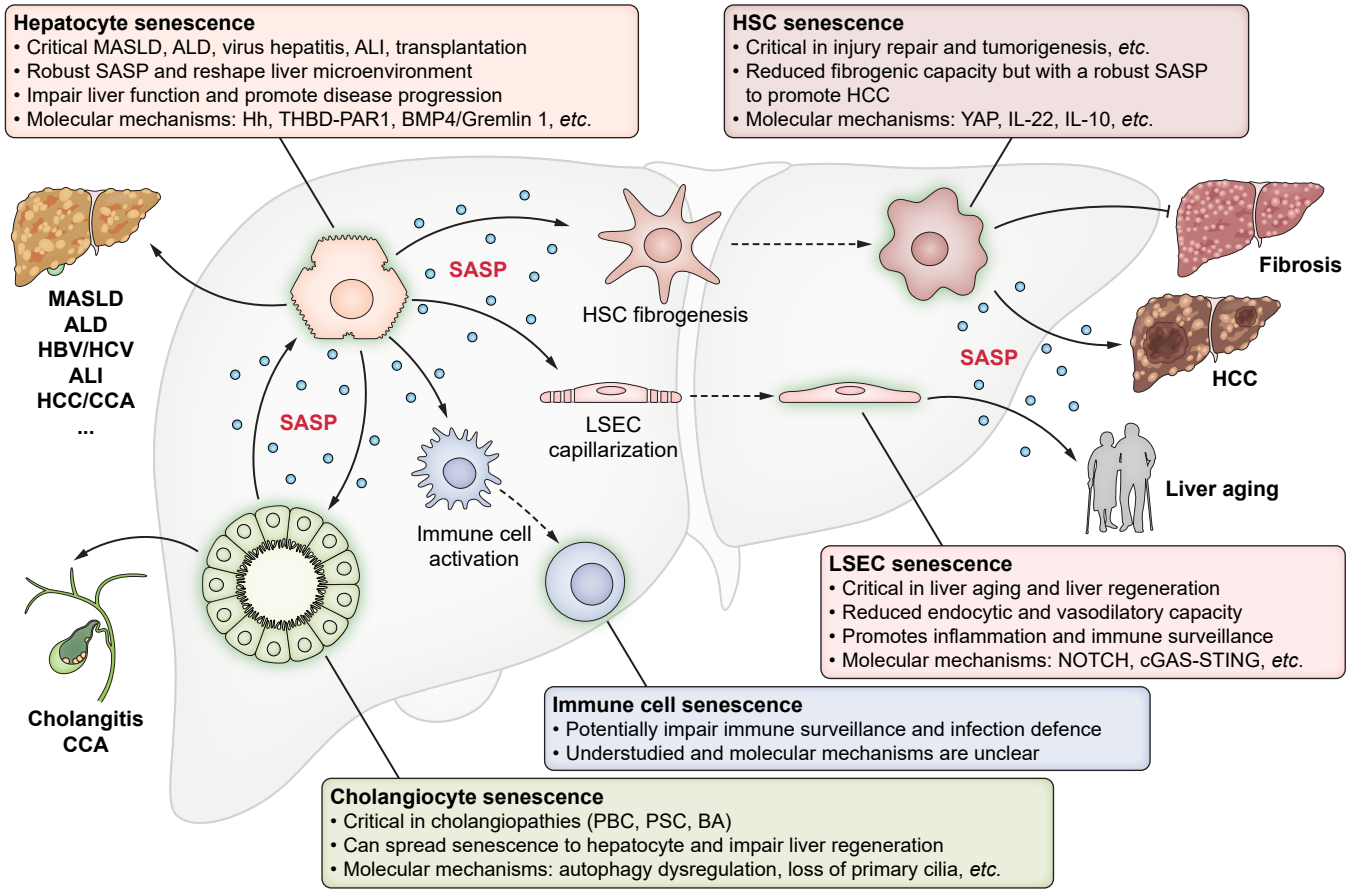
Hepatocyte senescence
• Critical MASLD, ALD, virus hepatitis, ALI, transplantation
• Robust SASP and reshape liver microenvironment
• Impair liver function and promote disease progression
• Molecular mechanisms: Hh, THBD-PAR1, BMP4/Gremlin 1, etc.
HSC senescence
• Critical in injury repair and tumorigenesis, etc.
• Reduced fibrogenic capacity but with a robust SASP to promote HCC
• Molecular mechanisms: YAP, IL-22, IL-10, etc.
MASLD
ALD
HBV/HCV
ALI
HCC/CCA
...
SASP
HSC fibrogenesis
Fibrosis
SASP
HCC
SASP
LSEC capillarization
Liver aging
Immune cell activation
Cholangitis
CCA
LSEC senescence
• Critical in liver aging and liver regeneration
• Reduced endocytic and vasodilatory capacity
• Promotes inflammation and immune surveillance
• Molecular mechanisms: NOTCH, cGAS-STING, etc.
Immune cell senescence
• Potentially impair immune surveillance and infection defence
• Understudied and molecular mechanisms are unclear
Cholangiocyte senescence
• Critical in cholangiopathies (PBC, PSC, BA)
• Can spread senescence to hepatocyte and impair liver regeneration
• Molecular mechanisms: autophagy dysregulation, loss of primary cilia, etc.

Fig. 2. Senescence across liver cell types: Diversity, mechanisms, and clinical implications. Hepatocyte senescence is a key driver in MASLD, ALD, viral hepatitis, ALI, post-transplantation settings, HCC and CCA, affecting disease progression through robust SASP production and remodelling of the hepatic microenvironment. It is regulated by signalling pathways such as Hedgehog, thrombomodulin-PAR1, and BMP4/gremlin1. Senescent HSCs arise during liver injury and exhibit context-dependent roles: while senescence limits their fibrogenic activity and facilitates fibrosis resolution and liver regeneration through SASP-mediated immune recruitment, their secretory profile can also drive inflammation and hepatocarcinogenesis, with regulation via YAP, IL-22, and IL-10. Cholangiocyte senescence is a defining feature of cholangiopathies including PSC, PBC, and BA, where it propagates senescence to neighbouring hepatocytes, impairs biliary regeneration, and promotes inflammation and fibrosis. Key mechanistic drivers include dysregulation of autophagy and loss of primary cilia. Senescent LSECs, which accumulate with age or injury, exhibit diminished endocytic and vasodilatory function, contribute to impaired liver regeneration, and promote inflammation and immune surveillance via SASP production, regulated in part by NOTCH signalling and the cGAS-STING pathway. Although less well characterised, senescent immune cells may further impair immune surveillance and foster chronic inflammation, highlighting the need for continued exploration of their roles in liver disease. ALD, alcohol-related liver disease; ALI, acute liver injury; BA, biliary atresia; CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; HSCs, hepatic stellate cells; LSECs, liver sinusoidal endothelial cells; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SASP, senescence-associated secretory phenotype.

The causal role of hepatocyte senescence in MASLD has been demonstrated in several key studies. In INK-ATTAC transgenic mice, where p16 senescent cells can be selectively ablated through drug-inducible activation of caspase, clearance of senescent hepatocytes led to significant reductions in hepatic steatosis in both aged mice and young mice fed a high-fat diet.[50] Similar improvements were observed following treatment with a senolytic cocktail of dasatinib and quercetin (D+Q) in db/db mice.[50] Building on these findings, our group recently identified a novel regulatory axis involving thrombomodulin–PAR1 signalling. Pharmacological inhibition of this pathway with vorapaxar, an FDA-approved PAR1 antagonist, significantly reduced hepatocyte senescence and ameliorated liver inflammation and fibrosis across multiple MASLD models.[51,52] Further mechanistic insights revealed that bone morphogenetic protein 4 (BMP4) suppresses, while its antagonist gremlin 1 promotes, hepatocyte senescence, inflammation, and fibrotic remodelling.[53] Likewise, inhibition of the SIRT1/PI3K/AKT/mTOR axis was found to alleviate hepatocyte senescence and attenuate disease progression.[54]

To develop more selective therapeutic strategies, we recently conducted a high-throughput chemical screen comparing cytotoxic effects on primary senescent *vs.* non-senescent hepatocytes and identified two copper-binding compounds, Dp44mT and DpC, as potent senolytics targeting senescent hepatocytes.[27] These agents accumulate in lysosomes, where they chelate endogenous copper to form redox-active complexes that disrupt lysosomal membranes and induce senescent cell death. In preclinical MASLD models, DpC treatment markedly reduced hepatocyte senescence and improved liver inflammation and fibrosis.[27] Collectively, these

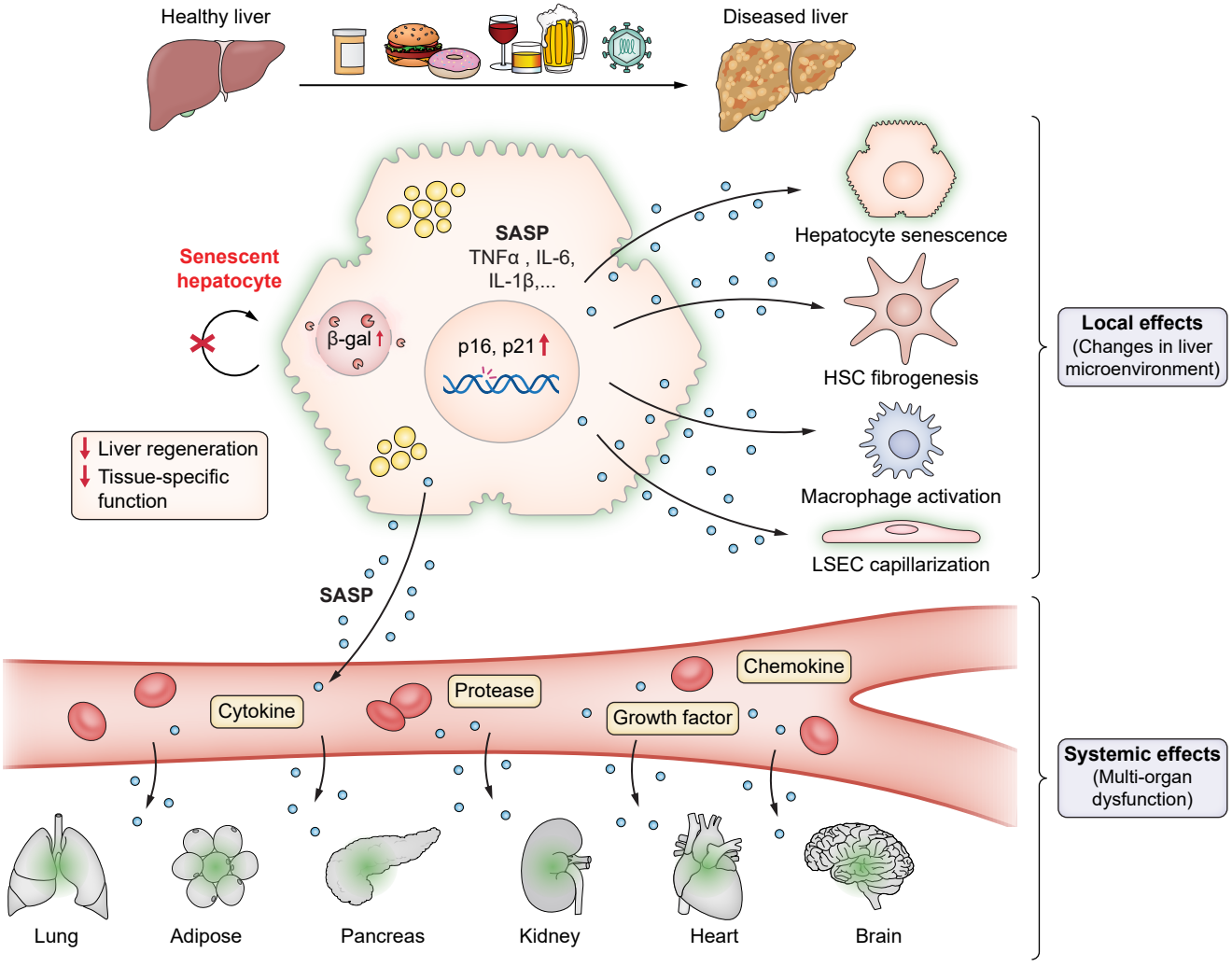

Fig. 3. Local and systemic consequences of hepatocyte senescence. Liver injury induced by high-fat diet, alcohol, drugs/toxins, or infections promotes the accumulation of senescent hepatocytes. These cells are characterised by elevated expression of cell cycle inhibitors (*e.g.* p16; p21), increased SA-β-Gal activity, and a robust SASP comprising cytokines, chemokines, growth factors, and proteases. Locally, the SASP impairs liver regeneration, disrupts tissue-specific functions, and propagates disease progression by inducing secondary senescence in neighbouring hepatocytes, activating HSCs, recruiting macrophages, and promoting LSEC capillarisation. Systemically, SASP factors enter the circulation and contribute to multi-organ dysfunction, affecting distant tissues including the pancreas, adipose tissue, kidneys, and heart. These effects highlight the pivotal role of hepatocyte senescence as a central mediator of both hepatic pathology and systemic dysfunction. HSCs, hepatic stellate cells; LSEC, liver sinusoidal endothelial cell; SA-β-Gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype.

findings reinforce that hepatocyte senescence is not merely a marker of disease severity but a key driver of MASLD pathogenesis, and underscore the therapeutic promise of precision senolytics that exploit cell-specific vulnerabilities, such as dysregulated metal homeostasis and organelle stress.

Hepatocyte senescence in ALD

Beyond MASLD, hepatocyte senescence is increasingly implicated in the pathogenesis of alcohol-related liver disease (ALD). Senescent hepatocytes in ALD display canonical features such as telomere shortening and elevated p21 expression, both of which correlate with more severe clinical outcomes.[55,56] Several upstream regulators have been implicated in modulating hepatocyte senescence in ALD, including ZNF281, NFATc4, microRNAs such as miR-34a and miR-194, and transcriptional regulators like YAP and FXR.[57–62] Liver-resident macrophages also modulate the senescent phenotype through paracrine signals.[63]

Alcohol-induced hepatitis (AH), a severe form of ALD, is marked by pronounced hepatocellular senescence. A recent transcriptomic study demonstrated progressive enrichment of senescence markers and pathways during the transition from ALD to AH, with partial resolution upon recovery.[64] The study also identified cytochrome c oxidase and proteasome complexes as potential mediators of ethanol-induced senescence.[64] Another study further confirmed elevated expression of senescence genes (*CDKN1A, CDKN2A*), robust p21 immunostaining, and enrichment of SASP components in AH livers.[65] Among these, hepatocyte-derived GDF15 was highly upregulated and correlated with senescence markers, clinical

severity, corticosteroid response, and 90-day mortality.[65] These findings suggest that senescence plays a central pathophysiologic role in AH and that GDF15 may serve as a prognostic biomarker. Additionally, prior work has shown that senescent hepatocytes exhibit loss of polarity, linking transcriptional changes to structural and functional disruption.[66]

Hepatocyte senescence in viral hepatitis

Hepatocyte senescence has also been implicated in the pathogenesis of viral hepatitis, particularly in chronic HBV and HCV infections.[67] In HBV infection, senescent hepatocytes demonstrate characteristic features such as p21-mediated G1 cell cycle arrest, telomere attrition, and nuclear enlargement.[68,69] Notably, cell cycle arrest, as measured by p21 expression, has been shown to correlate positively with inflammation and fibrosis. HBV replication appears to be restricted to actively proliferating hepatocytes, and the shift of HBcAg from the nucleus to the cytoplasm has been linked to the onset of cellular senescence [68,69] In HCV infection, senescent phenotypes are similarly observed, with increased expression of p21 and accumulation of oxidative DNA damage in hepatocytes.[70,71] The burden of liver senescence has been shown to correlate with the severity of fibrosis, reinforcing its role in chronic disease progression[61]. However, the identity of the predominant senescent cell populations in HCV-infected livers remains debated. Some studies have suggested that immune cells, particularly $CD3^+$ T cells, rather than hepatocytes, may account for a significant portion of the senescent cell pool in this context.[72,73] These findings highlight the complexity of cellular senescence in viral hepatitis and underscore the need for high-resolution, cell type-specific profiling to clarify its functional consequences and therapeutic relevance.

Hepatocyte senescence in acute liver injury and transplantation

In models of acute liver injury, hepatocyte senescence emerges rapidly and has been shown to impair tissue regeneration by fostering a pro-fibrogenic and pro-inflammatory microenvironment.[74,75] These detrimental effects appear to be mediated, at least in part, by TGFβ-dependent SASP signalling, which not only inhibits hepatocyte proliferation but also promotes immune activation and may contribute to systemic complications such as multi-organ dysfunction.[76–78] In the context of liver transplantation, the senescent status of host hepatocytes plays an additional role by modulating the engraftment efficiency and function of transplanted donor cells.[79] These findings suggest that hepatocyte senescence influences the regenerative capacity and immunologic milieu of the hepatic niche, with implications for transplant outcomes.

Together, these studies emphasise the pathological relevance of hepatocyte senescence across a spectrum of liver diseases and injury models. They also highlight an urgent need for hepatocyte-specific tools to study senescence *in situ*. Future research should prioritise the refinement of molecular biomarkers, a deeper understanding of the mechanisms that sustain hepatocyte senescence, and the development of targeted therapeutic strategies to mitigate its impact on liver health.

Senescence in cholangiocytes

Cholangiocyte senescence was first recognised in the context of chronic liver allograft rejection and obstructive cholangiopathies,[80] and is now established as a critical pathological feature across a broad spectrum of biliary diseases. Notably, this process is not limited to adult liver conditions; it is also observed in paediatric disorders such as biliary atresia, where senescence precedes fibrosis, suggesting it may act as an initiating event in disease progression.

Cholangiocyte senescence in PSC

In primary sclerosing cholangitis (PSC), senescent cholangiocytes are abundant and strongly correlate with disease severity and patient outcomes.[81,82] These cells express canonical senescence markers (p21, p16, γH2A.X) and have a robust SASP enriched in IL-1α, IL-6, IL-8, TGFβ, CCL2, and PAI-1.[81–83] A landmark study using the K19-CreERT2 *Mdm2*$^{-/-}$ mouse model, which induces cholangiocyte-specific p53-driven senescence, demonstrated that senescent cholangiocytes exacerbate hepatocyte senescence, promote biliary fibrosis, and impair tissue regeneration.[84] Mechanistically, the SASP facilitates immune cell recruitment, drives fibrogenesis, and propagates secondary senescence through N-Ras and TGF-β signalling.[83,84] Transcriptional regulators such as ETS1 and p300 enhance BCL-xL expression, enabling senescent cholangiocytes to evade apoptosis.[85,86] This resistance presents a therapeutic target: senolytics such as A1331852 and fisetin effectively clear senescent cholangiocytes in *Mdr2*$^{-/-}$ mice, leading to reduced disease severity.[87] Similarly, INK-ATTAC-mediated depletion of $p16^+$ cells also improves outcomes in PSC models.[87] Interestingly, microbial metabolites like ursodeoxycholic acid suppress cholangiocyte senescence, underscoring the role of microbiome-cholangiocyte senescence interactions in PSC pathogenesis.[88]

Cholangiocyte senescence in PBC

Senescence is also a prominent feature of primary biliary cholangitis (PBC), as evidenced by increased SA-βGal activity, elevated expression of p21 and p16, presence of DNA damage markers such as γH2A.X, and telomere shortening in cholangiocytes.[89,90] Notably, senescence burden is greater in advanced disease stages and correlates with poorer responses to ursodeoxycholic acid therapy.[91] Senescent cholangiocytes secrete chemokines like CCL2 and CX3CL1, promoting immune cell recruitment and hepatic inflammation.[92] These cells also upregulate autophagy markers (LC3, PDC-E2, p62),[93,94] suggesting a link between the dysregulation of autophagy and the senescence programme. Pharmacologic inhibition of autophagy using 3-methyladenine reduces both senescence and inflammatory chemokine production.[94] Notably, the same K19-CreERT2 *Mdm2*$^{-/-}$ mouse model used in PSC also recapitulates key features of PBC, reinforcing cholangiocyte senescence as a shared pathogenic mechanism.[84]

Cholangiocyte senescence in biliary atresia: Biliary atresia (BA) is a severe paediatric cholangiopathy characterised by progressive fibro-obliteration of the intrahepatic and extrahepatic bile ducts. Although less extensively studied than

in adult cholangiopathies, BA cholangiocytes also exhibit hallmarks of senescence, including increased SA-βGal activity, elevated p16 and γH2AX expression, and SASP components such as IL-8 and TGF-β1, as well as significant telomere shortening.[82,95–97] The intensity of these markers increases with disease progression, supporting a role for replicative and stress-induced senescence in BA pathogenesis.[86–88] Autophagy dysregulation may contribute as well, as evidenced by elevated p62 levels.[97] In a bile duct ligation model, treatment with human allogenic liver-derived progenitor cells reduced cholangiocyte senescence and improved liver pathology.[95] These findings offer preliminary but compelling support for the potential of senotherapeutic approaches in managing paediatric biliary cirrhosis.

Together, findings from PSC, PBC, and BA highlight cholangiocyte senescence as a shared pathological hallmark across diverse cholangiopathies. Although the upstream triggers and downstream effects differ by disease context, senescence consistently emerges as a central driver of inflammation, fibrosis, and impaired regeneration. Notably, a recent study has identified damage to cholangiocyte primary cilia, specialised sensory organelles, as a novel upstream driver of senescence, particularly under conditions of post-transplant ischaemic injury.[98] This finding opens new avenues for intervention, as restoring ciliary integrity or targeting cholangiocyte senescence could enhance regenerative responses and reduce biliary complications in transplant and disease settings.[98]

Senescence in hepatic stellate cells

HSC, the liver's resident pericytes, are essential regulators of extracellular matrix remodelling, fibrogenesis, and overall liver homeostasis. In response to liver injury, quiescent HSCs transdifferentiate into activated myofibroblast-like cells characterised by increased proliferation, contractility, and deposition of fibrotic proteins such as collagen. While this activation is crucial for acute tissue repair, sustained activation contributes to chronic liver fibrosis.[99] Notably, a fraction of these activated HSCs enters a state of cellular senescence. This senescent phenotype, once considered a passive byproduct of injury, is now increasingly appreciated as a dynamic modulator of fibrosis resolution, tissue regeneration, and tumourigenesis.[99]

Senescent HSCs have been identified in various liver diseases and are characterised by classical senescent markers, including p21, p16, SA-βGal activity, and DNA damage foci (*e.g.* γH2A.X).[100] Functionally, senescent HSCs exhibit stable cell cycle arrest and reduced fibrogenic activity, suggesting a protective role in limiting fibrosis[100-98]. In mouse models, disruption of p53/p21 signalling accelerates fibrosis, underscoring the anti-fibrotic potential of HSC senescence.[26,101–105] Mechanistically, this effect is mediated by downregulation of fibrotic genes (*e.g. Col1a1, Acta2*) and upregulation of immune ligands that promote immune-mediated clearance of senescent cells.[26,101–105] Recent studies have identified key pathways that induce HSC senescence during liver fibrosis, including the Hippo-YAP axis[26] and cytokines such as IL-22[102] and IL-10.[106] In acute injury contexts like partial hepatectomy, a subpopulation of HSCs rapidly acquire a senescent phenotype, secrete IL-6 and CXCR2 ligands, and promote regenerative signalling.[107] Intriguingly, depletion of these cells impairs regenerative capacity, highlighting their beneficial role in acute repair contexts.[107]

However, the impact of HSC senescence is highly context-dependent and not uniformly beneficial. Senescent HSCs often develop a robust SASP, characterised by pro-inflammatory cytokines (IL-6, IL-8), chemokines (CCL2, CXCL1), matrix metalloproteinases (MMP2, MMP9), and TGF-β.[99,100] This secretome reshapes the liver microenvironment by promoting immune infiltration, sustaining inflammation, and inducing secondary senescence in neighbouring non-senescent HSCs.[99,100] Interestingly, senescent HSCs express the urokinase plasminogen activator receptor (uPAR), which has been successfully exploited for targeted clearance using uPAR-specific chimeric antigen receptor (CAR)-T cells in carbon tetrachloride- and MASH-induced fibrosis models.[40,108] Natural killer (NK) cells and M1 macrophages also preferentially eliminate senescent HSCs, linking immune surveillance to fibrosis resolution[94,109,110].

Senescent HSCs are also increasingly implicated in liver tumourigenesis. Early studies showed colocalisation of senescence markers (p21, p16, γH2AX, 53BP1) and SASP components (IL-6, IL-8) with αSMA in cirrhotic livers and in HCC.[101,111,112] Tumour-promoting SASPs can be induced by bile acid metabolites such as deoxycholic acid[111,113] or by hepatocytic loss of FBP1,[114] facilitating HCC development. Senolytic therapies, such as D+Q, ABT-263 and other emerging agents, have shown efficacy in clearing senescent HSCs and reducing obesity-associated HCC in preclinical models.[114,115] Moreover, IL-33 release via gasdermin D–dependent mechanisms has been shown to suppress anti-tumour immunity by impairing $CD8^+$ T cell responses in MASH-associated HCC.[116] Nevertheless, conflicting findings persist: for instance, p53 deletion in HSCs decreases senescence but increases tumour incidence,[117] while compounds such as epigallocatechin gallate promote HSC senescence but inhibit HCC progression.[118] These findings emphasise the need for precise, cell type-specific and temporally controlled models to elucidate the dual roles of HSC senescence in liver carcinogenesis.

Looking ahead, key challenges include defining the heterogeneity and temporal dynamics of senescent HSCs. Whether these cells represent a uniform population or consist of distinct subtypes with divergent functions remains unclear. Emerging technologies, including single-cell and spatial transcriptomics, are expected to clarify these aspects. Ultimately, therapeutic strategies that leverage transient senescence to suppress fibrosis, followed by targeted senolytic clearance, may offer a compelling approach to halt or reverse chronic liver disease progression while minimising oncogenic risk.

Senescence in other liver cell types

In addition to hepatocytes, cholangiocytes, and HSCs, cellular senescence has also been observed in other non-parenchymal liver cell types, including LSECs, Kupffer cells, and infiltrating immune populations. Although less extensively studied, these senescent populations are increasingly implicated in reshaping the hepatic microenvironment through mechanisms including vascular remodelling, immune dysregulation, and fibrogenesis.[3] Among these, senescent LSECs are relatively well

characterised. Age-related morphological changes in LSECs include loss of fenestrations, decreased porosity, endothelial thickening, and deposition of a basal lamina, features that mirror capillarisation in non-fenestrated vascular beds.[3] These structural alterations are accompanied by impaired scavenger functions, reduced endocytic capacity, and a slightly pro-inflammatory phenotype.[3] Mechanistically, recent studies have implicated cGAS-STING signalling as a key pathway in LSEC senescence,[119] and shear stress can induce senescence via the Notch–SIRT1–p21/p16 axis, thereby impairing liver regeneration following partial hepatectomy.[120] In contrast, the roles of senescent immune cells remain poorly defined, though they are speculated to disrupt immune surveillance and contribute to chronic inflammation[3]. While the relevance of senescence in these cell types continues to emerge, their functional contributions and upstream regulators remain incompletely understood. Several recent reviews have thoroughly summarised this evolving area of research;[3,6,48,121] therefore, they are not discussed in detail in this review.

Hierarchical and cross-lineage propagation of senescence

Emerging evidence suggests that senescence can propagate beyond the initially affected cell through paracrine and juxtacrine signalling, contributing to tissue-wide dysfunction. Primary senescence arises in cells directly exposed to stressors, while secondary senescence is induced in adjacent cells via factors secreted in the SASP. Foundational work by Acosta and Gil demonstrated that TGF-β and IL-1α are key mediators of this paracrine senescence *in vitro.*[122] More recently, Notch signalling has been identified as a juxtacrine mechanism of senescence transmission, particularly in hepatic and fibroblast models, where Notch activation in neighbouring cells reinforces the senescent phenotype independent of soluble SASP cues.[123–125] *In vivo* studies, including those in hepatic contexts, have confirmed that senescence and SASPs can spread across liver cell types, for example, from hepatocytes to macrophages or LSECs, and from cholangiocytes to hepatocytes, through coordinated Notch and TGF-β signalling.[76,84,126] In some settings, this cascade can extend to tertiary senescence, affecting entire tissue niches.[77,78] These multicellular interactions reshape the liver microenvironment, driving fibrosis, inflammation, and carcinogenic potential. Understanding the hierarchical and cross-lineage propagation of senescence will be critical for designing therapies that can interrupt these circuits and prevent systemic tissue dysfunction.

In summary, despite growing recognition of its importance, accurately identifying and functionally characterising senescent cells in the liver remains a major challenge. This is due to the marked heterogeneity in senescence phenotypes and the lack of lineage-specific, definitive biomarkers. Current detection methods often rely on p16 or p21 expression, which are neither exclusive to senescence nor uniformly expressed across cell types.[127,128] Moreover, distinguishing transient stress responses from irreversible cell cycle arrest is an ongoing limitation. As senescence can arise via both cell-intrinsic damage and paracrine signals, future research must prioritise context-specific models that account for cell type, disease stage, and spatial dynamics. Developing such models, alongside robust molecular and functional tools, will be essential for mapping senescence at high resolution and realising the full therapeutic potential of senescence-targeted interventions in chronic liver disease.

Senescence in liver cancer: a double-edged sword

HCC, the most common form of primary liver cancer, accounts for 75–85% of liver cancer cases and represents a growing global health burden.[129] Despite advances in surveillance and therapy, HCC remains difficult to treat because of its tendency to recur, drug resistance, and the complex interplay of intracellular and extracellular factors that shape its tumour microenvironment.[129] Cellular senescence has emerged as a key regulator in liver carcinogenesis, acting as a double-edged sword, both suppressing and promoting tumour development depending on timing, context, and cell type.

Senescence induction serves as a powerful tumour-suppressive mechanism, halting the proliferation of damaged or pre-malignant hepatocytes through p53/p21-and p16-mediated growth arrest. In parallel, senescent cells secrete a range of SASP factors that activate immune surveillance and promote the clearance of pre-malignant cells, a process termed “senescence surveillance”.[130] For instance, oncogene-induced senescence in hepatocytes elicits $CD4^+$ T cell-mediated immune responses that prevent malignant transformation.[131] Reactivation of p53 in murine liver tumours similarly reinstates senescence and triggers tumour regression through the recruitment of neutrophils, macrophages and natural killer cells.[132] These findings underscore that hepatocyte senescence is not merely a passive growth arrest but an active, immunologically engaged barrier against liver tumour initiation.

However, this tumour-suppressive barrier can be breached. In settings of liver damage and regeneration, such as partial hepatectomy or thioacetamide-induced chronic injury, hepatocytes undergoing oncogene-induced senescence may evade immune surveillance and undergo malignant transformation into HCC.[133] Chronic inflammation impairs the clearance of senescent cells, enabling their persistence and eventual reprogramming into tumour-promoting cells. Senescent hepatocytes recruit $CCR2^+$ myeloid cells to facilitate their immune clearance, and loss of CCR2 disrupts this surveillance, accelerating hepatocarcinogenesis. Yet, in established HCC, tumour cells inhibit myeloid maturation, converting them into immunosuppressive cells that suppress NK cell activity and promote tumour growth.[134] Clinical observations also support this concept; hepatocytes from patients who developed HCC exhibited greater DNA damage and senescence compared to those from patients with cirrhosis who remained tumour free.[135] Moreover, the SASP, while initially protective, can paradoxically foster a pro-tumourigenic microenvironment. SASP factors such as IL-6, IL-1β, and CCL2 promote inflammation, angiogenesis, and proliferation of neighbouring cells.[130] In HSCs, senescence induced by gut microbiota-derived metabolites like deoxycholic acid and lipoteichoic acid leads to a pro-inflammatory SASP that supports HCC growth.[136–138] Similarly, hepatic macrophages activated by hepatocyte-derived SASP contribute to immune evasion and tumour progression.[139] These findings underscore that

senescence is not merely a static endpoint but a dynamic state that can shift from anti-to pro-tumourigenic under chronic stress or immune dysfunction. Adding to this complexity, senescence is increasingly linked to the emergence of aggressive, treatment-resistant tumour clones. Senescence-associated reprogramming may give rise to stem-like cancer cells capable of driving recurrence.[140,141] Recent work has demonstrated that titrating down oncogenic Ras signalling enables senescent hepatocytes to evade immune surveillance, promoting tumourigenesis *in vivo.*[142] This aligns with the "Wnt-just right" hypothesis, wherein finely tuned signalling intensity governs senescence escape and cancer risk in both liver and colon models.[143,144] These insights highlight how subtle modulation of oncogenic pathways in senescent cells can profoundly influence tumour initiation and progression. Notably, senescent cells in HCC can express immune checkpoint molecules like PD-L1, enabling them to resist T cell-mediated clearance even in the presence of SASPs. Blockade of the PD-1/PD-L1 axis rejuvenates immune surveillance of senescent cells and mitigates age-related hepatic phenotypes in mouse MASLD models, highlighting a potential therapeutic avenue.[145]

Similar mechanisms may operate in cholangiocarcinoma (CCA), the second most common primary liver malignancy. Recent studies reveal that senescence also contributes to CCA pathogenesis and progression. EZH2, a polycomb group protein upregulated in CCA, represses senescence by hypermethylating the p16 promoter, thereby promoting malignant transformation.[146] In intrahepatic CCA, senescence-associated long non-coding RNAs were used to develop a machine learning-based prognostic signature that stratifies patients by survival, immune landscape, and therapeutic response.[147] Senescent cancer-associated fibroblasts marked by high CAV1 expression are also linked to worse clinical outcomes.[148] Moreover, in combined HCC-CCA, senescence and IL-6 trans-signalling drive tumour formation from hepatic progenitor cells, and senolytic therapy (*e.g.* ABT-737) reduces tumour burden by disrupting this axis.[149]

Together, these findings illustrate that senescence in liver cancer is highly context-specific – varying by tumour subtype, disease stage, and microenvironmental cues. While senescence serves as a critical tumour-suppressive mechanism, its persistence and associated SASP can rewire the tissue landscape toward a tumour-promoting state. Targeting senescence plasticity with senotherapies, immune checkpoint modulation, or epigenetic reprogramming represents a promising approach for treating both HCC and CCA.

Senotherapies for liver diseases: promise and pitfalls

Senotherapeutic strategies, encompassing senolytics and senomorphics, have emerged as promising approaches for combating liver diseases by either eliminating senescent cells or mitigating their harmful secretory profiles.[150] However, accumulating evidence suggests that the efficacy of these strategies for liver diseases is highly dependent on the targeted cell type, the specific agent employed, and the disease context, with outcomes ranging from therapeutic benefits to adverse effects (Fig. 4).

Senolytics

A growing body of evidence supports the therapeutic potential of senolytics in the treatment of liver diseases. In the context of transplantation, senolytic preconditioning, either through recipient treatment with ABT-737 or by cold storage of donor livers with senolytics, such as ABT-737 or D+Q, preserved biliary regenerative capacity and improved graft viability.[151] Similarly, reducing senescence burden in recipients with ABT-737 prior to transplantation enhanced donor hepatocyte proliferation and improved engraftment efficiency,[79] highlighting the promise of modulating the hepatic niche using serotherapies to optimise regenerative therapies in clinic. In a mouse model of partial hepatectomy, ABT-737 treatment also disrupted aberrant p21 expression, thereby restoring regenerative capacity in adult livers.[152] In a mouse model of PSC, removal of senescent cholangiocytes using the BCL-xL inhibitor A-1331852 or the flavonoid fisetin attenuated fibrosis and inflammatory signalling.[85] Likewise, in MASLD mouse models, treatment with ABT263[153] or the senolytic cocktail of D+Q[50] also decreased hepatocyte senescence and alleviated disease severity. Consistently, clearance of senescent HSCs using uPAR-targeted CAR-T cells not only reduced MASLD severity but also improved liver function and restored systemic homeostasis,[108] underscoring the therapeutic potential of senescence-targeted strategies beyond disease cessation. Collectively, these studies provide strong evidence that targeting senescent cells can improve liver disease outcomes.

However, despite these encouraging results, broad translation of senolytics remains challenging. D+Q, though effective in some metabolic models, failed to eliminate senescent hepatocytes *in vitro* and showed no benefit in models of acute liver injury, such as acetaminophen-induced hepatotoxicity[75] and bile duct ligation.[95] Likewise, BCL-xL inhibitors such as A-1331852 and ABT263 were also ineffective for lowering liver senescent burdens or ameliorating fibrosis in a carbon tetrachloride-induced liver injury model.[26] More concerningly, D+Q exacerbated HCC in both the diethylnitrosamine/high-fat diet and xenograft models.[154,155] These findings underscore the limitations of broad-spectrum senolytics and reinforce the need for cell type- and context-specific senolytic strategies.[39,156]

Recent studies have revealed the importance of timing and disease context in senolytic efficacy. In MASLD-associated HCC models (STAM mice), early administration of the liver-targeted senolytic 753b, a BCL-xL/BCL-2 proteolysis targeting chimera (PROTAC), during the steatosis phase failed to reduce senescence or prevent HCC. In contrast, delayed administration during the MASH phase significantly reduced senescent hepatocyte burden, fibrosis, and tumour development. However, once HCC was established, 753b treatment lost efficacy.[157] In ALD models, ABT-263 successfully reduced senescent hepatocytes and HSCs but paradoxically increased plasma alanine aminotransferase and triglyceride levels, suggesting that non-selective senolysis can exacerbate liver injury under certain conditions.[158] By contrast, nicotinamide, an NAD^+ precursor that can suppress senescence, effectively reduced SASP production and liver injury, and improved lipid metabolism.[158]

Senolytic efficacy also varies by tissue type and sex. In aged mice, D+Q effectively reduced senescence markers in

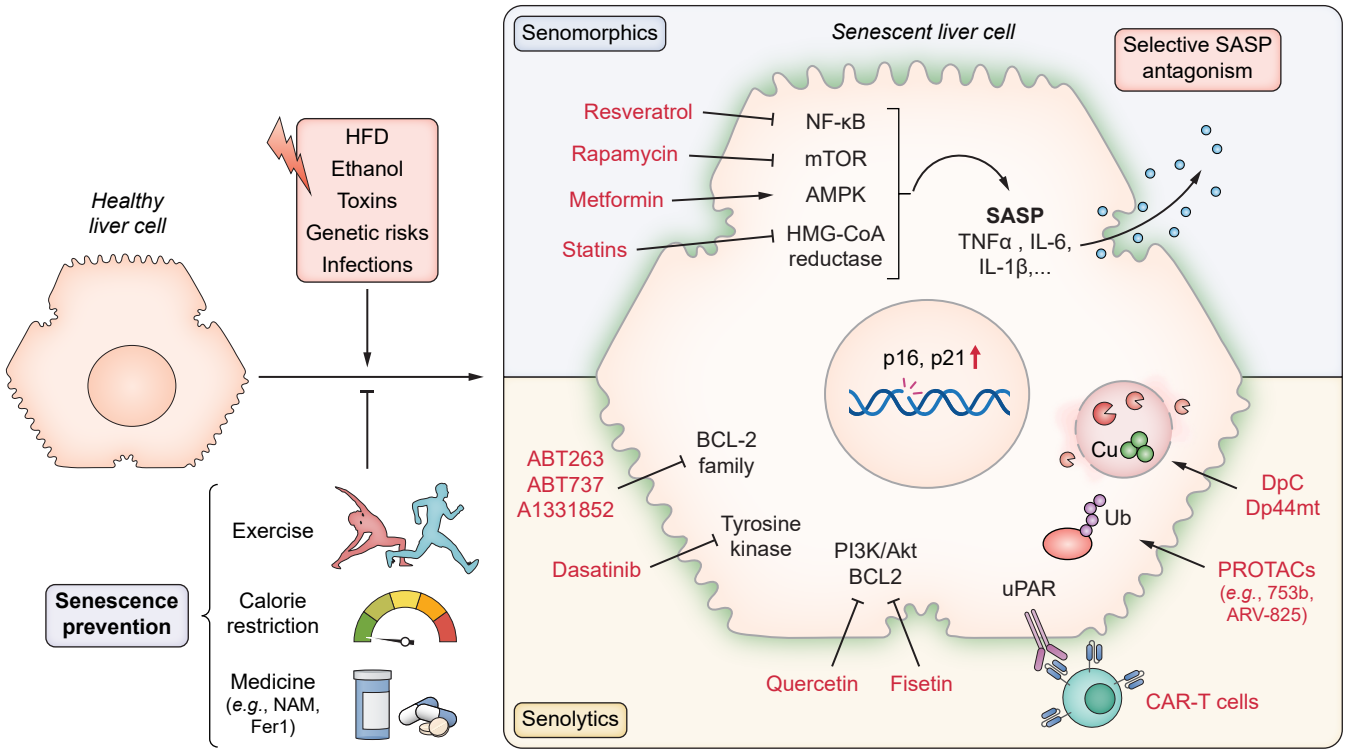

Fig. 4. Senotherapies for liver senescence. This schematic illustrates the major pathways and therapeutic strategies for the prevention and treatment of liver senescence. Diverse insults, including HFD, ethanol, toxins, infections, and genetic risk factors, can initiate cellular stress responses in healthy hepatic cells, ultimately leading to senescence characterised by DNA damage, cell cycle arrest (via p16 and p21), and secretion of pro-inflammatory SASP factors. Preventive strategies such as exercise, calorie restriction, and agents like NAM and ferroptosis inhibitors (*e.g.* Fer-1) may delay or prevent senescence onset. In senescent liver cells, senomorphics (*e.g.* metformin, statins, rapamycin, resveratrol) suppress SASP production by modulating key pathways including AMPK, mTOR, and NF-κB, without inducing senescent cell death. Senolytics (*e.g.* ABT263, ABT737, A1331852, dasatinib, quercetin, fisetin, and DpC/Dp44mT) selectively eliminate senescent cells by targeting vulnerabilities such as the BCL-2 family, PI3K/Akt signalling, and lysosomal copper accumulation. Emerging precision strategies, such as PROTAC-based senolytics (*e.g.* 753b, ARV-825) and uPAR-targeted CAR-T cells, offered enhanced cell type specificity and reduced off-target toxicity, and have shown better efficacy in preclinical models of liver diseases. Collectively, these approaches offer a multipronged framework for mitigating chronic liver diseases driven by pathogenic senescence. CAR-T, chimeric antigen receptor T cells; HFD, high-fat diet; NAM, nicotinamide; PROTAC, proteolysis targeting chimera; SASP, senescence-associated secretory phenotype.

adipose tissue and improved metabolic function but had minimal impact on senescence burden in liver or skeletal muscle.[159] Sex-specific differences further complicate the picture: in multiple organs, including the liver, fisetin treatment improved metabolism and reduced SASP markers in male mice, whereas D+Q treatment worsened metabolic health and increased senescence in female mice. No beneficial effects were observed in D+Q-treated males or fisetin-treated females.[160] Furthermore, recent studies have revealed functional heterogeneity among senescent cell populations. G2-arrested endothelial cells and fibroblasts exhibited higher levels of senescence markers, secreted more IL-6, and were more susceptible to ABT263-induced apoptosis compared to G1-arrested cells.[161] These findings highlight that even within a single cell type, the senescent state can dictate therapeutic responsiveness.

Together, these studies illustrate both the promise and pitfalls of senolytic therapies in liver disease. They also emphasise the need for precision senolytic strategies tailored to disease context, cell type, sex, and senescent cell state to optimise outcomes while minimising unintended harm.

Senomorphics

In addition to senolytics, senomorphics (agents that suppress the deleterious SASP without inducing senescent cell death) represent an important alternative therapeutic strategy. Several compounds with senomorphic properties have shown promise in preclinical liver disease models and are already clinically available, making them attractive candidates for repurposing. Rapamycin, one of the most extensively studied senomorphics, modulates the SASP through inhibition of the mTOR pathway.[162] In a mouse model where hepatocyte senescence was induced via oncogenic $Nras^{G12V}$, rapamycin did not reduce senescent cell burden, but significantly suppressed SASP expression and immune cell infiltration.[163] In the Mdm2 liver senescence model, rapamycin prevented the spread of systemic senescence by inhibiting the SASP, highlighting its potential to modulate both local and distal senescence-driven pathology.[77] Similarly, resveratrol also extends lifespan in various model organisms[150] and suppresses the SASP in hepatocyte senescence models,[164] largely via activation of the SIRT1 pathway and inhibition of NF-κB

signalling. Metformin, a widely used antidiabetic agent, inhibits SASP production through activation of AMPK and suppression of NF-κB signalling.[165] Notably, in aged LSECs, metformin restores endothelial fenestration and mitigates vascular ageing.[166] These findings align with emerging epidemiological data linking metformin use to reduced HCC incidence,[167] suggesting that its senomorphic actions may contribute to its cancer-protective effects. Statins also modulate endothelial function via enhanced nitric oxide availability and KLF2 signalling, which have been shown to reduce portal hypertension and liver fibrosis.[168–170] Interestingly, observational studies have associated statin use with reduced liver cancer risk,[171,172] raising the possibility that these effects may partially stem from attenuation of senescence-associated pathways. Beyond these agents, IL-33, a key SASP component secreted by senescent HSCs, has recently emerged as a therapeutic target. IL-33 blockade suppressed HCC development in preclinical models,[116] highlighting the translational relevance of SASP modulation as a strategy to counter liver disease progression and malignancy.

Despite their promise, senomorphics carry notable limitations. Unlike senolytics, which can often be administered intermittently, senomorphics typically require continuous or frequent dosing to sustain efficacy, raising concerns about patient compliance and long-term safety. Moreover, targeting individual SASP factors may be insufficient due to the complex and redundant nature of SASP components; inhibiting one factor/pathway may allow compensatory activation of others, preserving the pro-inflammatory environment. Indeed, clinical trials targeting specific SASP elements such as TNF-α or IL-1β in patients with severe AH have largely failed to improve outcomes and, in some cases, increased mortality due to infectious complications.[173,174] Thus, while senomorphics offer a less aggressive alternative to direct senolytic strategies, they require thoughtful dosing regimens, careful target selection, and comprehensive safety evaluations. Future strategies may benefit from broad SASP modulation or combinatorial approaches that integrate senomorphics with intermittent senolytics to enhance efficacy.

Targeting additional senescence hallmarks

Beyond pharmacological agents, lifestyle interventions such as exercise and caloric restriction have demonstrated senescence-modulating potential.[175,176] In preclinical models of high-fat diet-induced MASLD and in aged rodents, both interventions reduced hepatic steatosis, senescence burden, and inflammation.[50,177] Moderate exercise also attenuated age-related liver injury, senescence, and tumourigenesis.[178] These benefits have been linked to transcriptional activation of enzymes involved in the tryptophan-to-NAD^+ pathway, resulting in increased hepatic NAD^+ levels and enhanced activity of the NAD^+-dependent deacetylase SIRT1. Elevated SIRT1 activity, in turn, promotes deacetylation of key transcriptional regulators, including NF-κB (p65) and PGC-1α, which are involved in inflammation and mitochondrial metabolism, respectively.[178] Supporting this, a recent study showed that nutritional supplementation with nicotinamide, which restores intracellular NAD^+ levels, reduced hepatocyte senescence and ameliorated liver injury in mouse models of ALD.[158] In parallel, mitochondria-directed therapies, such as mitophagy activators and mitochondrial-targeted antioxidants (*e.g.*, MitoQ, MitoTEMPO), are being explored to reverse senescence-associated mitochondrial dysfunction and reduce SASP production.[179] Telomerase-based strategies have also shown promise: in telomerase-deficient mice, telomere dysfunction impaired liver regeneration and accelerated cirrhosis, whereas adenoviral delivery of the telomerase RNA component restored telomere function, alleviated cirrhotic pathology, and improved liver function.[180] Given the heterogeneity of senescent phenotypes across liver cell types, combining these targeted interventions with senolytics or senomorphics may enhance efficacy and selectivity for chronic liver disease treatment.

Taken together, these findings emphasise that the efficacy of senotherapeutic interventions in liver disease is profoundly dependent on cell type, therapeutic agent, timing, and disease context. While broad-spectrum senolytics hold therapeutic potential, their lack of specificity may lead to unintended effects, particularly in settings of ongoing injury or malignancy. Conversely, although senomorphics provide a subtler alternative by modulating SASP without inducing cell death, their effects are often modest and require sustained exposure. Moreover, targeting individual SASP factors has proven largely ineffective in advanced liver disease and may even worsen outcomes. These challenges highlight the urgent need for precision senotherapies that are cell type-specific, context-sensitive, and mechanistically aligned with disease biology..

Key challenges and future directions in targeting liver senescence (Box 2)

Characterisation of senescent liver cells *in situ*

A major barrier to advancing the field of liver senescence is the limited characterisation of senescent cells directly isolated from disease-relevant liver tissue. To define the molecular identity and functional state of senescent liver cells, it is essential to isolate and profile these cells from clinically relevant models, and ideally, from human patient samples. While recent advances in single-cell and single-nucleus transcriptomics have enabled transcriptomic profiling of senescent cells within their native tissue context,[27,40,181] a more comprehensive understanding requires multimodal phenotyping. This includes integration of proteomic signatures, protein localisation patterns, and metabolic alterations associated with senescence and the SASP. In addition, spatial transcriptomic and proteomic methods are increasingly important for mapping the interactions between senescent and non-senescent cells, particularly in contexts where primary senescence may propagate to secondary or tertiary populations. These multi-dimensional approaches are critical for developing precise biomarkers and designing cell type-targeted therapeutic strategies.

Addressing the dynamic and heterogeneous nature of senescence

Senescent cells are inherently dynamic and heterogeneous, complicating their detection and therapeutic targeting. Conventional markers like p16 and p21 lack specificity and cannot

Box 2. Key future priorities in liver senescence research.

- Advance senescence detection: Move beyond single markers (*e.g.* p16, p21) by developing and validating multiplex molecular signatures (*e.g.* SHGS) for more accurate and specific *in vivo* identification of senescent liver cells.
- Characterise cell type- and disease-specific senescence: Isolate and profile senescent liver cells directly from clinically relevant disease models and human livers using integrated transcriptomic, proteomic, and secretomic approaches.
- Develop non-invasive biomarkers: Identify and validate circulating senescence-associated biomarkers to enable patient stratification, real-time monitoring, and assessment of senotherapeutic efficacy.
- Uncover mechanisms of senescence induction and maintenance: Define the molecular drivers and sustainers of hepatic senescence (*e.g.* Hippo-YAP, Hedgehog, dysregulated copper and iron homeostasis) to reveal novel therapeutic vulnerabilities.
- Clarify local and systemic effects: Investigate how senescent cells reshape the hepatic microenvironment and contribute to systemic aging, metabolic dysfunction, and multi-organ dysfunction in chronic liver diseases.
- Enhance safety and specificity of senotherapies: Develop next-generation, cell type-specific senolytics (*e.g.* copper-targeted DpC/Dp44mT, liver-tropic PROTACs like 753b and ART-825, CAR-T cells targeting senescent antigens) to minimise off-target toxicity and maximise therapeutic precision.
- Integrate senomorphics and lifestyle strategies: Explore safer alternatives to eliminate or suppress senescence, including NAD^+ boosters (*e.g.* NAM), metformin, exercise, and dietary interventions, aiming for long-term control of the SASP and preservation of regenerative potential.

CAR-T, chimeric antigen receptor T cells; NAM, nicotinamide; PROTAC, proteolysis targeting chimera; SASP, senescence-associated secretory phenotype.

distinguish irreversible senescence from transient cell cycle arrest.[127,128] To address this challenge, we recently developed a SHGS, which robustly tracks with MASLD progression and clinical outcomes, outperforming previously reported senescence signatures.[27] Single-nucleus RNA-sequencing analyses confirmed that SHGS(+) hepatocytes exhibit the full spectrum of senescence hallmarks.[27] Notably, GLP-1 receptor agonist treatment reduced SHGS expression in a MASH mouse model,[27] suggesting that this class of drugs may exert senescence-modulating effects. Although hepatic cell types share core senescence mechanisms, such as p53/p21 activation, SASP secretion, and mitochondrial dysfunction, they also exhibit distinct, lineage-specific features. For instance, cholangiocyte senescence often involves Notch/TGF-β-mediated signalling, while senescent HSCs are characterised by uPAR expression and matrix-remodelling programmes. These differences support the feasibility of cell-type-targeted senotherapies, an emerging strategy exemplified by uPAR-targeted CAR-T cells for senescent HSCs[108] and DpC/Dp44mT for selective hepatocyte senolysis.[27] These findings underscore the need to move beyond single markers and embrace multiplexed molecular signatures to accurately identify and characterise senescent liver cells.

Elucidating molecular drivers and maintainers of senescence

Identifying the molecular pathways that initiate and sustain cellular senescence is essential for developing rational and effective therapeutic strategies. Recent studies have begun to uncover critical regulators across various liver cell types. For instance, suppression of the Hippo-YAP signalling pathway induces HSC senescence during fibrosis,[26] while inhibition of Hedgehog signalling in hepatocytes promotes senescence by disrupting mitochondrial fitness through downregulation of thymidine phosphorylase.[182] The BMP4-gremlin 1 axis also plays a pivotal role in modulating hepatocyte senescence in MASLD.[53] Our recent high-throughput screen of 2,100 bioactive compounds identified key vulnerabilities in senescent hepatocytes. The most selectively cytotoxic compounds targeted three main pathways: the proteasome, histone deacetylases, and the PI3K/mTOR/autophagy axis, all of which are known to be essential for senescent cell survival.[27] Beyond signalling cascades, metabolic stressors such as ferroptosis, driven by iron overload, and lysosomal copper accumulation also act as potent inducers of hepatocyte senescence. Notably, pharmacological inhibition of these pathways using agents such as ferrostatin-1 or copper-binding senolytics (DpC and Dp44mT) significantly reduced senescence burden and improved liver pathology in preclinical models.[27,46] Together, these findings lay a strong foundation for precision senotherapy by highlighting actionable vulnerabilities specific to senescent liver cells.

Developing non-invasive biomarkers to quantify senescence burden

Non-invasive biomarkers are urgently needed to quantify senescence burden and monitor responses to senotherapeutic interventions. Circulating SASP components, including IL-23R, CCL5, GDF15, RAGE, VEGFA, PARC, and MMP2, have emerged as candidate markers.[183,184] Our recent work also identified GDF15 as a SASP factor secreted by SHGS(+) hepatocytes.[27] Notably, circulating GDF15 levels correlated strongly with hepatic senescence burden and clinical outcomes in patients with MASLD,[27] underscoring its potential as a blood-based biomarker for patient stratification and for monitoring therapeutic efficacy. Moving forward, a systematic effort to define a comprehensive panel of "senescence-associated secreted biomarkers" will be critical for developing precision diagnostics and enabling personalised senescence-targeted interventions.

Examining local and systemic impact of liver senescence

Emerging evidence has highlighted the profound local and systemic consequences of hepatic senescence (Fig. 3). Early studies demonstrated that senescent HSCs, through their SASP, contribute to a pro-tumourigenic microenvironment. By modulating immune responses, interacting with the gut microbiome and promoting oncogenic signalling, senescent HSCs accelerate fibrosis and facilitate HCC development. Clearance of senescent HSCs ameliorated fibrosis and inhibited tumour progression, establishing HSC senescence as

a pathogenic driver in chronic liver disease.[111,112,114,116,185] Building on these findings, our recent studies have revealed that hepatocyte senescence exerts even broader effects, both within the liver and systemically. Senescent hepatocytes, through their distinct SASP, activate HSCs, recruit inflammatory macrophages, and induce vascular remodelling, thereby accelerating liver disease progression.[27] Beyond the liver, our recent work also demonstrated that hepatocyte senescence activity, measured by SHGS, correlates with dysfunction in distant organs such as the kidney, heart, pancreas, and adipose tissue. Importantly, targeting senescent hepatocytes improved not only MASLD pathology but also systemic metabolic health.[27] Consistent with these findings, other studies have also shown that liver-derived senescence signals can propagate to distant tissues, contributing to multi-organ failure through TGFβ-mediated mechanisms.[77,78] Interestingly, senescence in the adipose tissue[186] and skin[187] has also been shown to influence brain function and systemic homeostasis, reinforcing the emerging concept of cellular senescence as an "endocrine disruptor" of organismal health. While senolytic strategies have focused on the elimination of senescent cells, the long-term fate of these cells remains poorly understood and warrants further study. Whether senescent cells are irreversibly arrested, can evolve into distinct functional states, or under certain conditions revert to a non-senescent phenotype remains a topic of active investigation. Clarifying these trajectories, clearance *vs.* reprogramming, will be crucial for optimising senescence-targeted therapies and understanding their systemic impact.

Ensuring the safety and efficacy of senotherapies

Despite the therapeutic promise of senotherapies, safety concerns remain a major translational barrier. Broad-spectrum senolytics such as dasatinib, navitoclax (ABT-263), and BCL-xL inhibitors frequently cause off-target toxicities, including thrombocytopenia, neutropenia, and impaired wound healing due to their indiscriminate elimination of proliferating or non-senescent cells.[156,188] Navitoclax, in particular, has been associated with serious haematological adverse events in clinical trials.[189–191] These effects are of particular concern in patients with chronic liver disease, who often suffer from consumptive thrombocytopenia due to hypersplenism and are already at risk of major bleeding events, such as variceal haemorrhage. Furthermore, although SASP factors promote chronic inflammation, they can also play beneficial roles in tissue repair and immune surveillance; thus, indiscriminate clearance of senescent cells may impair regenerative responses or exacerbate immunosuppression.[156,188] While intermittent dosing regimens are being explored to mitigate toxicity, establishing durable, tissue-specific safety profiles remains an unmet need. In parallel, emerging studies support a "one-two punch" strategy in cancer therapy: first inducing senescence to halt tumour proliferation, followed by selective senolytic clearance. In HCC, senescence can be triggered through CDC7 inhibition in TP53-mutant tumours, rendering cells susceptible to mTOR inhibition or agents like sertraline.[192] Likewise, combined CDK4/6 and XPO1 inhibition induces senescence and creates a vulnerability to CRBN-based PROTACs such as ARV-825.[193] However, work from the Bernards group also cautions that senescent cells escaping clearance may acquire more aggressive, drug-resistant phenotypes. These findings underscore the importance of precise therapeutic sequencing and rigorous modelling of tumour evolution to ensure that senescence induction does not inadvertently promote malignancy.[194] Together, these challenges highlight the urgent need for next-generation precision senotherapies. Emerging strategies include senolytic PROTACs (*e.g.* 753b; PZ15227; ARV-825) or prodrugs that enhance specificity and tissue targeting;[157,193,195] and immune-based approaches, such as CAR-T cells engineered to recognise senescence-associated antigens.[108,196,197] Moving forward, integrating high-resolution molecular profiling with rational therapeutic design will be essential to harness the full potential of senescence-targeted therapies in liver disease.

Concluding perspectives

Over the past decade, remarkable progress has deepened our understanding of how cellular senescence contributes to liver disease, systemic dysfunction, and aging-related comorbidities. It is now evident that senescence is not merely a passive marker of liver injury but an active mediator of disease, shaping local hepatic pathology and exerting far-reaching systemic effects. However, translating senescence biology into effective clinical therapies remains challenging. The heterogeneity of senescent cells, the lack of specific biomarkers, and the potential risks associated with broad-spectrum senolytics underscore the need for next-generation precision senotherapies. Encouragingly, the first clinical trial evaluating senolytic therapy in patients with MASLD and fibrosis using D+Q is currently underway (NCT05506488), reflecting growing momentum toward clinical translation. Moving forward, a combination of strategies, including cell type-specific senolytic development, rigorous mechanistic dissection of senescence drivers, advanced biomarker discovery, and exploration of systemic senescence networks, will be critical to harness the full therapeutic potential of targeting senescence. With the rapid advance of single-cell technologies, organoid systems, and rational drug design, the future holds exciting opportunities to redefine how we diagnose, monitor, and treat chronic liver diseases through the lens of cellular senescence. Precision senotherapy may not only transform the management of MASLD and related liver disorders but also offer a unified strategy to combat the broader spectrum of aging-related diseases.

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Abbreviations

AH, alcohol-induced hepatitis; ALD, alcohol-related liver disease; ALI, acute liver injury; AMPK, AMP-activated protein kinase; BA, biliary atresia; BDL, bile duct ligation; CAR-T, chimeric antigen receptor T cell; CCA, cholangiocarcinoma; CDK, cyclin-dependent kinase; cGAS–STING, cyclic GMP–AMP synthase–stimulator of interferon genes pathway; DDR, DNA damage response; D+Q, dasatinib + quercetin; ECM, extracellular matrix; HALPCs, human allogenic liver-derived progenitor cells; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HFD, high-fat diet; Hh, Hedgehog signaling; HSC, hepatic stellate cell; IL, interleukin; LMP, lysosomal membrane permeabilization; LSEC,

liver sinusoidal endothelial cell; MMP, matrix metalloproteinase; NAM, nicotinamide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; OIS, oncogene-induced senescence; PAR1, protease-activated receptor 1; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PROTAC, proteolysis targeting chimera; ROS, reactive oxygen species; SA-β-gal, senescence-associated β-galactosidase; SAHF, senescence-associated heterochromatin foci; SASP(s), senescence-associated secretory phenotype(s); SHGS, senescent hepatocyte gene signature; TGFβ, transforming growth factor beta; uPAR, urokinase plasminogen activator receptor; YAP, Yes-associated protein.

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Conflict of interest

The authors declare no competing interests. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

KD – Conceptualized and collated the work, wrote and edited the manuscript. DSU – Conceptualized the work. NR – Edited the final manuscript. AMD – Conceptualized and supervised the work and edited the final manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) to correct grammatical errors and enhance clarity and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary data

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Author names in bold designate shared co-first authorship

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